REMARKS

CLAIM AMENDMENTS

The claims have been amended to recite animals, cells, and methods relating to transgenic mice. Specifically, claims 1-2, 5-6, 9, 13-18, 38-39, and 42-49 have been amended to recite that the transgenic nonhuman animal is a transgenic mouse. In addition, claims 19-21, 50-53, and 55 directed to a cortical cell culture have been amended to recite derivation from a transgenic mouse. Also, claims 27-34 have been amended to recite that the embryonic stem cell (and derived blastocyst) is a mouse embryonic stem cell. Claims 22-26 and 54 have been amended to recite methods of using a transgenic mouse. Claims 35-37 have been amended to recite methods of generating a transgenic mouse. Support for the claim amendments are found throughout the specification.

Claim 22 has been further amended to more clearly define the invention. Specifically, claim 22 has been amended to recite that the protease is a protease other than BACE-1. Support for the amendment is found throughout the specification, for example, at paragraphs [54] and [61]. Claim 22 was also amended to recite that the transgenic mouse lacks a functional allele of a BACE-1 gene. Support for the amendment is found throughout the specification, for example, at paragraphs [49] and [56].

The claim amendments are made solely in an effort to advance prosecution and are made without prejudice, without intent to acquiesce in any rejection of record, and without intent to abandon any previously claimed subject matter.

New claims 53-55 are directed to a cortical cell culture and method wherein the peptide is β-amyloid peptide. Support for the new claims are found throughout the specification and particularly at, for example, paragraphs [36]-[40], [61]-[74], [75]-[79], and [81] –[85].

THE OFFICE ACTION

The 35 USC § 101 Rejection

Claims 1-6, 9, and 13-52 have been rejected under 35 USC § 101, because the claimed invention allegedly lacks patentable utility. Specifically, the Office alleges that the claims lack either a specific or substantial utility. Applicants note that claims 29, and 40-41 have been cancelled rendering the rejection moot as to those claims. With respect to the other claims, Applicants respectfully traverse the rejection.

To properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a *prima facie* showing that the clamed invention lacks utility, and (B) provide sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. A *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements:

> (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established;
>
> (2) Support for factual findings relied upon in reaching this conclusion; and
>
> (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

Further, whenever possible, the Examiner should provide documentary evidence regardless of publication date (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

Applicants submit that the Office has failed to make a *prima facie* showing of lack of utility because the Office has failed to satisfy paragraphs (2) and (3) of the required elements. While the Office makes various factual allegations that the claimed invention lacks specific and substantial utility, it provides no evidentiary basis whatsoever to support its allegations. Further, even if, for the sake of argument, documentary evidence is not available, the Office has failed to explain the scientific basis for its factual conclusions. Thus, the Office has not met its initial burden of showing more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicants would be specific and substantial.

Despite the fact that Applicants believe the Office has not made a *prima facie* showing of lack of utility, the Applicants provide the following discussion to assert the specific and substantial utility of the claimed invention.

Specific Utility

An invention has specific utility if the identified use or application is specific to the subject matter claimed. As explained in the specification, one of the cardinal features of Alzheimer's disease (AD) is the deposition of plaques comprised of aggregated beta-amyloid peptides (Aβ) in the brain (specification at paragraph [07]). Aβ is produced from its precursor protein, APP, by proteolytic processing at its N and C termini by β- and γ-secretase enzymes, respectively (specification at paragraph [07]). Due to the critical role that β-secretase (e.g., BACE-1) plays in the onset, development, and maintenance of Alzheimer's disease, transgenic BACE-1 knockout animals, i.e., comprising at least one nonfunctional allele of a BACE-1 gene, are unique tools for the further study of Alzheimer's disease and particularly for the development of therapeutics to treat AD (specification at paragraph [61]).

Thus, the claims to transgenic mice and methods of using the mice have a specific utility in that the claimed mice and methods can be used to screen for inhibitors of β-secretase activity, inhibitors of other proteases, and assay for side effects of the

inhibitors, all of which are useful in identifying therapeutics for the treatment and/or prevention of Alzheimer's disease.

In particular, the claimed transgenic BACE-1 knockout mouse and screening assay can be used to screen for an inhibitor of the production of a specific peptide (i.e., recognized by an antibody that recognizes residues 13-28 of Aβ), which peptide is associated with Alzheimer's disease (specification at paragraphs [07] ad [61]). Thus, the claimed transgenic mouse and corresponding screening assay is useful to specifically identify an inhibitor compound that is useful to specifically treat Alzheimer's disease. The disclosure of a specific use to identify a compound for the treatment of a specific disorder (AD) is clearly distinguishable from "situations where the applicant merely indicates that an invention may prove useful without identifying with specificity why it is considered useful ... or indicating that a compound may be useful in treating unspecified disorders." Given that the Applicants have identified with specificity why the invention is useful, the claimed transgenic BACE-1 knockout animal and corresponding screening assay method have specific utility.

Applicants note that the MPEP clearly states that screening assays, such as the screening assays claimed in the present invention, "have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds)." MPEP §2107.01 I. In the present case, the transgenic mouse and screening assay is useful in analyzing potential therapeutic compounds for the treatment of Alzheimer's disease.

The Office argues that the claimed transgenic animal and assay do not have specific utility because "using the animal to screen for proteases other than β-secretases that cause the production of a protein that is recognized by an antibody, which recognizes certain residues in A/β, the Alzheimer's disease related peptide is not specifically directed at a specific protein". (Office Action dated June 28, 2004, page 3). The Office compares the utility of the present invention to the utility of a "gene probe" or "chromosome marker" that would not be considered to be specific in the absence of a disclosure of a specific DNA target. (Office Action dated June 28, 2004, page 3).

However, in contrast to the Office's allegation and comparison with a gene probe that does not disclose a specific DNA target, the present invention clearly discloses a specific target for the inhibitor compound, which is a non-BACE-1 protease that causes the production of an Aβ peptide that is specifically recognized by an antibody that recognizes residues 13-28 of Aβ. Such protease targets may include, for example, γ-secretase, presenilin-1, presenilin-2, and BACE-2, among others (specification at paragraphs [07, [51] and [61]).

The Office also alleges that the method of analyzing potential side-effects for an inhibitor of beta-secretase using the transgenic BACE-1 knockout animal does not have specific utility "because the identification of other effects that a β-secretase inhibitor would have on an animal is not directed to (sic) any particular effect. Like the gene probe discussed above, there is no specific target of the assay." (Office Action dated June 28, 2004, page 3).

However, comparing the specific utility of a claim directed to a method of analyzing potential side-effects for an inhibitor of beta-secretase to the specific utility of a claim directed to a polynucleotide is an improper comparison because the two claims differ completely in form and purpose. The specific utility of the presently claimed method using the transgenic animal is to analyze the side-effect(s) (i.e. toxicity) of an inhibitor of beta-secretase by measuring a biological change in the transgenic animal in the presence or absence of the inhibitor. The transgenic animal is an in vivo model that is uniquely suited for such use. Thus, the specific utility of the claimed method is comparable to that of a screening assay used to determine the side effect(s) of a specific compound (i.e., rather than the compound itself). Such a screening assay has a "clear, specific and unquestionable utility" in that it is useful in analyzing the side effect(s) of a specific compound.

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Substantial Utility

A claimed invention has substantial utility if it defines a "real world" use. According to the MPEP, "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility". MPEP §2107.01 I. The term "benefit to the public" is not interpreted "to mean that products or services based on the claimed invention must be 'currently available' to the public in order to satisfy the utility requirement." MPEP §2107.01, citing *Brenner v. Manson*, 383 U.S. 519, 534-35 (1966).

The claims to transgenic mice and methods of using the mice have a substantial utility in that the claimed mice and methods can be used to identify therapeutics for the treatment and/or prevention of Alzheimer's disease.

According to the MPEP, "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a real world context of use in identifying potential candidates for preventative measures or further monitoring." MPEP §2107.01 I. In the present case, the claimed transgenic BACE-1 knockout mouse and screening assay can be used to screen for an inhibitor of the production of Aβ peptide (i.e., peptide recognized by an antibody that recognizes residues 13-28 of Aβ), which peptide is associated with Alzheimer's disease. Importantly, the claimed transgenic BACE-1 knockout mouse is uniquely useful to identify those inhibitors of a protease other than BACE-1, such as γ-secretase, presenilin-1, presenilin-2, and BACE-2, among others. Thus, the claimed transgenic mouse and corresponding screening assay have a "real world" use in "an assay that measures the presence of a material" (Aβ peptide) "which has a stated correlation to a predisposition to the onset of a particular disease condition" (Alzheimer's disease). Accordingly, the claimed transgenic BACE-1 knockout mouse and corresponding screening assay method have substantial utility.

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The Office argues that the transgenic mouse and methods for screening for an inhibitor of an Aβ peptide lack substantial utility because there is no real world use disclosed for the results of the assay, i.e., the specification does not state for what purpose the peptide would be used. The Office concludes that identifying an inhibitor and screening for a peptide would require further experimentation on the identified inhibitor and peptide. (Office Action, page 4).

However, the specification clearly teaches that the real world use of the transgenic BACE-1 knockout animal and the screening assay is to identify inhibitors of Aβ peptide production for the purpose of identifying potential therapeutics for the treatment of Alzheimer's disease. First, the specification clearly teaches that the production of Aβ peptide in the brain correlates with Alzheimer's disease (specification at paragraph [07]). Second, the specification clearly teaches that inhibitors of proteases which cause the production of Aβ peptide, such as BACE-1 among others, can be used as therapeutics in the treatment of Alzheimer's disease (specification at paragraphs [09] and [61]). Based on this teaching, one skilled in the art would understand that the Aβ peptide serves as a "marker" for AD and thus the purpose or "real world" use of a screening assay to identify inhibitors of Aβ peptide production is to identify potential therapeutics for the treatment of AD.

In arguing that "the specification does not state for what purpose the peptide would be used", and also stating that "screening for a peptide" would require further experimentation, it appears that the Office does not understand the invention. The utility of the transgenic BACE-1 knockout animal and the screening assay is not in "screening for a peptide", but rather in screening for an inhibitor of Aβ peptide production for the purpose of identifying potential therapeutics for AD.

Further, the Office's conclusion that the transgenic animal and screening assay do not have substantial utility because "identifying an inhibitor and screening for a peptide would require further experimentation on the identified inhibitor and peptide" is

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misguided. As previously discussed, the real world utility of identifying an inhibitor is to identify a potential therapeutic for the treatment of AD. The MPEP clearly explains that "identifying potential candidates for preventative measures or further monitoring" is a real world use and further recognizes that products or services based on the claimed invention do not have to be currently available to the public in order to satisfy the utility requirement (i.e., the necessity of further experimentation does not preclude a finding of substantial utility). MPEP §2107.01, *Brenner v. Manson*, 383 U.S. 519, 534-35 (1966).

In addition, the claimed transgenic BACE-1 knockout mouse can be used to analyze potential side-effects (e.g., determine the toxicity profile) of an inhibitor of beta-secretase by exposing the transgenic mouse to an inhibitor of beta secretase and measuring a change in the level of at least one component of the transgenic mouse wherein such change indicates a potential side effect (specification at paragraph [62]).

The Office alleges that the transgenic animal and methods for identifying other effects that a β-secretase inhibitor would have on the transgenic animal lack substantial utility "because there is no real world use for the so identified proteases". The Office further alleges "the specification does not describe how one would use the identified inhibitors, or how this information could be used." (Office Action, page 4).

First, the asserted utility of the claimed method is not directed to use of the protease. Instead, the asserted utility is the analysis of potential side-effects of a protease (i.e., beta-secretase) inhibitor. Second, as previously discussed, the real world use of an identified inhibitor is as a potential therapeutic for the treatment of AD. Thus, the claimed method for analyzing side effects of an inhibitor has a real world use for determining the side effects of a potential therapeutic for the treatment of AD, for example, the likelihood of toxicity (specification at paragraphs [52] and [62]). One skilled in the art would further realize that any identified side effects of an inhibitor in the transgenic animals would be reasonably predictive of side effects of a therapeutic in humans. See MPEP §2107.03 III.

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For all of the reasons discussed above, the pending claims have specific and substantial utility. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §101 rejection.

The 35 USC § 112, First Paragraph, Rejection

Claims 1-6, 9, and 13-52 have been rejected under 35 USC § 112, first paragraph, as allegedly failing to teach one skilled in the art how to make and use the claimed invention. Applicant respectfully traverses the rejection.

The Office alleges that since the claims are not supported by either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. However, for all of the reasons discussed above, the specification clearly teaches one skilled in the art how to use the claimed invention.

The Office further alleges that the asserted utility of identification of inhibitors of other proteases involved with the onset of Alzheimer's disease does not constitute a specific utility as it is not specific to BACE-1 knockout animals. The Office states that "[s]uch identification can be accomplished by any other animal, which exhibits proteolytic cleavage of APP associated with Alzheimer's disease." (Office Action dated January 25, 2005, page 3). Contrary to the Office's allegation, the transgenic BACE-1 knockout mouse is uniquely and specifically designed to identify inhibitors of proteases other than BACE-1. Given that the transgenic BACE-1 knockout mouse does not have a functional BACE-1, any observed proteolytic cleavage of APP must necessarily be caused by a protease other than BACE-1. It follows that any inhibition of observed proteolytic cleavage must reflect the inhibition of a protease(s) other than BACE-1.

In contrast, the identification of inhibitors of proteases other than BACE-1 can not be accomplished using any other animal that exhibits proteolytic cleavage of APP, as the Office suggests, because such animal would have a functional BACE-1 (see specification at paragraph [63]). In view of the fact that BACE-1 is the primary protease responsible for a majority of the proteolytic cleavage of APP in the brain (specification at paragraphs

[69]-[74]), it would be difficult to determine whether the observed inhibition of proteolytic cleavage of APP reflects the inhibition of BACE-1 or the inhibition of another protease. Accordingly, the use of the claimed transgenic mouse to identify inhibitors of proteases other than BACE-1 involved with the onset of Alzheimer's disease is specific to the transgenic mouse and methods.

In addition, the Office alleges that the claims lack a substantial utility because there is no disclosure as to how the results would be used without further experimentation. However, contrary to the Office's allegation, the specification teaches that the results of identifying inhibitors of proteases that cleave APP (i.e., proteases that cause the production of Aβ) is the identification of therapeutics for the treatment and/or prevention of Alzheimer's disease (specification at paragraphs [09] and [61]). As discussed previously, products or services based on the claimed invention do not have to be currently available to the public in order to satisfy the utility requirement. With respect to any identified therapeutics, the Federal Circuit has found utility for therapeutic inventions despite the fact that an Applicant is at the very early stage in the development of a therapeutic. *Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985). In this regard, the Federal Circuit has stated that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995); *Scott v. Finney*, 34 F.3d 1058 (Fed. Cir. 1994).

For the reasons stated above, the claimed invention has a specific and substantial utility such that one skilled in the art would know how to use the claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 USC §112, first paragraph, rejection, based on lack of utility.

The Office further argues that the claims are not enabled because they contain subject matter which allegedly was not described in the specification in such a way to as to enable one skilled in the art to make and/or use the invention. More particularly, the

Office asserts that, while the specification is enabling the production of BACE-1 null mice, the specification is not enabled for the breadth of nonhuman animals claimed.

Solely in an effort to advance prosecution, Applicants have amended the claims to be directed to transgenic mice comprising at least one nonfunctional allele of a (BACE-1) gene. In view of the claim amendments, the rejection is moot. Accordingly, Applicants respectfully request withdrawal of the 35 USC §112, first paragraph, rejection.

CONCLUSION

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,
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Date: June 27, 2005

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